
Molecular analyses of neurogenic defects in a human pluripotent stem cell model of fragile X syndrome.

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Public Summary:

New research suggests that common pathways are altered in many neurodevelopmental disorders including autism spectrum disorder; however, little is known about early molecular events that contribute to the pathology of these diseases. The study of monogenic, neurodevelopmental disorders with a high incidence of autistic behaviours, such as fragile X syndrome, has the potential to identify genes and pathways that are dysregulated in autism spectrum disorder as well as fragile X syndrome. In vitro generation of human disease-relevant cell types provides the ability to investigate aspects of disease that are impossible to study in patients or animal models. Differentiation of human pluripotent stem cells recapitulates development of the neocortex, an area affected in both fragile X syndrome and autism spectrum disorder. We have generated induced human pluripotent stem cells from several individuals clinically diagnosed with fragile X syndrome and autism spectrum disorder. When differentiated to dorsal forebrain cell fates, our fragile X syndrome human pluripotent stem cell lines exhibited reproducible aberrant neurogenic phenotypes. Using global gene expression and DNA methylation profiling, we have analysed the early stages of neurogenesis in fragile X syndrome human pluripotent stem cells. We discovered aberrant DNA methylation patterns at specific genomic regions in fragile X syndrome cells, and identified dysregulated gene- and network-level correlates of fragile X syndrome that are associated with developmental signalling, cell migration, and neuronal maturation. Integration of our gene expression and epigenetic analysis identified altered epigenetic-mediated transcriptional regulation of a distinct set of genes in fragile X syndrome. These fragile X syndrome-aberrant networks are significantly enriched for genes associated with autism spectrum disorder, giving support to the idea that underlying similarities exist among these neurodevelopmental diseases.

Scientific Abstract:

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